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Multiscale Modeling Framework for Lung Airways Inflammation

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Abstract

Better understanding of the acute/chronic inflammation in airways is very important in to order avoid lung injuries for patients undergoing mechanical ventilation. Inflammation is a complex and dynamic process triggered by many mechanisms within the lung and involves multiple scales starting from organ level to cellular level. In this study, a multiscale modeling framework is being developed to address the cellular inflammation due to mechanical ventilation at the organ level. The developed multiscale modeling framework is illustrated through a case study to investigate inflammatory responses at the alveolar sac during mechanical ventilation. The simulation results showed that high tidal volume (1400 cc) during mechanical ventilation can cause tissue injury due to high concentration of activated immune cells. These results can be further extended to investigate the effects of mechanical ventilation parameters.

Keywords: Inflammation; Multiscale Modeling; Simulations; Acute Lung Injury; Ventilation

1. Introduction

Inflammation has been recognized as a major integral component for most of the acute and chronic diseases. Inflammation can be initiated within the body as an innate process or by external factors such as infections and trauma. Inflammation is a complex and dynamic process, and involves nonlinearity and stochasticity. Without the inflammation, the harmful stimuli cannot be removed and the healing process cannot occur. However, an over-expression or under-expression of inflammatory responses can lead to severe consequences, such as Multiple Organ Dysfunction Syndrome (MODS), which is characterized by sequential organ failure. Acute lung injury (ALI) is typically one of the first manifestation of MODS. It can be triggered by external stimuli such as pathogens or from

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inflammatory mediators produced from various other processes ranging from other damaged organs or to blood transfusions to even the biomechanical forces of mechanical ventilation itself.

Inflammatory responses in the airway induced by mechanical ventilation are complex processes dealing with a length scale that ranges from ~ 1 nm for cytokine proteins to ~ 1 cm for the airway. Responses in one length scale highly depend on responses in another length scale. Airway displacements from the organ level affect the distributions of stresses and strains in the tissue level. These stresses and strains in the tissue level affect the level of proinflammatory cytokines [1] at the cellular level. The inflammatory responses at the cellular level, in turn, alter the mechanical properties of airway tissue in the tissue level; e.g., stiff smooth muscle layer in the asthma airway [2]. The alteration of material properties of airway tissue leads to a change in material properties of the airway in the organ level. It is clear that no single model can cover a factor of 10^7 in a spatial scale. A practical approach is to develop many models that cover a limited range of the spatial scale and to develop a technique that links these models together to investigate airway inflammation induced by mechanical ventilation.

Due to the complexity of biomechanics problems, several investigators are developing multi-scale models, see for example, Refs. [3, 5]. Fredberg and Kamm [5] reviewed the stress transmission in the lung from cell to organ level. There is no multiscale modeling of lung inflammation due to mechanical ventilation in the existing literature. In this study, a multiscale modeling framework is being developed to address the cellular inflammation due to mechanical ventilation at the organ level. The developed multiscale modeling framework is demonstrated through a case study to investigate inflammatory responses at the alveolar sac during mechanical ventilation.

2. Multiscale Inflammation Modeling

The multiscale modeling framework being developed in this study uses the organ-level model to drive inflammatory responses at the cellular level. The inflammatory responses from the cellular-level model, in turn, modulate changes in material properties at tissue and organ levels. During each specific time step, the airway displacements at each location in the organ-level model are first determined by performing a finite element analysis with the fluid-solid interaction (FSI) algorithm. The results of the airway displacements at each node of the organ-level model are then used to define the applied boundary conditions for the tissue-level model. Strains in each tissue layer are calculated employing the finite element analysis. These strains in each layer are then transferred to the cellular-level model. Change in the recruiting rate of the activated immune cells is associated with the transferred strains from the tissue-level model.

The number of healthy and damaged cells from the cellular-level model, in turn, affects the material properties of the airway tissue at the tissue-level model. The changes in material properties at the tissue-level model are then transferred to the organ-level model. The airway displacements at each location in the organ-level model are then determined using these new material properties. These procedures are repeated until the specific time period is reached. Each of the modeling techniques at organ, tissue and cellular levels are briefly described below.

Organ Level: The organ level models focuses on the organ, say either whole lung or airways or part of the lung – alveolar sacs and investigates the response due to mechanical ventilation. The response is calculated through fluid-solid interactions algorithm of the organ level model, and by continuum models of fluid and solid mechanics approaches. The governing equations for airflow are Navier-Stokes equations on a moving mesh with incompressible flow and use the principles of mass and momentum conservation. The governing equations for movement of airways due to mechanical ventilation are the time-dependent structural equations. The numerical solutions of the interaction between airflow and airway walls during mechanical ventilation was implemented using two software packages, ANSYS and ANSYS CFX [6].

ANSYS is a general-purpose finite element (FE) software for structural modeling, and ANSYS CFX is general-purpose computational fluid dynamics (CFD) software for modeling fluid flows. The governing equations for transient airflow are Navier-Stokes equations on a moving mesh with the assumption of incompressible flow was used. These equations govern the principles of mass and momentum conservation and are given as,

Conservation of mass

$$\frac{\rho_g}{\sqrt{g}}\frac{\partial}{\partial t}\left(\sqrt{g}\right)+\rho_g\frac{\partial}{\partial x_j}\left(u_j-\frac{\partial \tilde{x}_j}{\partial t}\right)=0 \tag{1}$$

Conservation of momentum

$$\frac{\rho_g}{\sqrt{g}}\frac{\partial}{\partial t}\left(\sqrt{g}\,u_i\right)+\rho_g\frac{\partial}{\partial x_j}\left[\left(u_j-\frac{\partial \tilde{x}_j}{\partial t}\right)u_i\right]=-\frac{\partial p}{\partial x_i}+\mu\frac{\partial^2 u_i}{\partial x_j^{\,2}} \tag{2}$$

In these equations, $\tilde{x}_i$ represents the moving mesh location, $\sqrt{g}$ is the metric tensor determinate of the transformation, i.e., the local computational control-volume size, ρ_g is fluid density, p is fluid pressure, μ is fluid viscosity, and u is fluid velocity.

The governing relations for movement of the airway wall during mechanical ventilation are the time-dependent structural equations and are described below as,

Equation of motion

$$\frac{\partial \sigma_{ij}}{\partial x_j}+F_i=\rho\frac{\partial^2 u_i}{\partial t^2} \tag{3}$$

Constitutive relations

$$\sigma_{ij}=C_{ijkl}\varepsilon_{kl} \tag{4}$$

In the equation above, σ is the stress in each direction, F is the body force, ρ is density, u is the displacement, C is the elasticity tensor, and ε is the strain in each direction.

The fluid-structure interaction (FSI) procedures began by solving the flow equations to obtain fluid pressure. Structural equations are then solved for the displacement using the fluid pressure as an external force. The flow equations are solved again to obtain the fluid pressure after the structural displacement changes the fluid boundaries. This loop continues until both fluid pressure and airway displacement converge for each time period. Additional details can be found in a study by Koombua et al. [7].

Tissue Level Model: The tissue level model focuses on the airway tissue morphology and material properties, and investigates the stress/strain response due to airway displacements from the organ level model. The standard finite element method (FEM) approach was used in order to solve equations for stress analysis. More details about the tissue level model can be found in a recent study by Pidaparti and Koombua [8]. The strain levels obtained from the tissue level model are used in the cellular level model.

Cellular Level Model: The cellular level model focuses on the biochemical processes at the cellular/subcellular levels, and is based on discrete modeling using cellular-automata (CA) modeling. The CA model was composed of two species: epithelial cell and immune cell. The CA model was constructed on two-dimensional square lattice where each lattice site represented one epithelial cell. The immune cell was mobile and can move from one lattice to another. Therefore, the square lattice was like the tissue of immobile epithelial cells which was patrolled by the mobile immune cells. The CA was updated synchronously based on specific rules. The ratio of the number of damaged cells to healthy cells was obtained through the cellular-level model. The details of the CA model are given in Ref. [9].

3. A Case Study

In order to demonstrate the multiscale modeling framework described in the earlier section, a simplified model of the alveolar sac from the literature [10] was chosen for the computational simulation. The alveolar sac has a diameter of 500 μm. The alveolar duct diameter was 200 μm and the entrance length was 100 μm [10]. The alveolar sac was assumed to be homogeneous and isotropic material with the Young's modulus of 80 kPa and Poisson's ratio of 0.45 as it is composed mainly of a single layer of an alveolar epithelium. The boundary conditions at the tissue-level model were airway displacements at each location from the organ-level model. The strain levels in the epithelial layer from the tissue-level model are then used to study inflammatory responses at the cellular level. The cellular automata (CA) model for inflammatory responses due to strain levels was implemented using MATLAB. The simulation was performed on a lattice of 44 × 44 sites which represented a tissue area of 0.88 × 0.88 mm^2, a total surface area of the simplified alveolar sac model. The initial population of immune cells was 40 cells. The periodic boundary conditions were used for the simulation. The initial conditions for the CA model were randomly placed immune cells. Only one immune cell can occupy one lattice site. Each epithelial cell was randomly assigned its lifespan. The simulations were carried out with the following physiological assumptions: 1) only healthy epithelial cells are able to divide and 2) strain levels do not affect inactivated immune cells.

The ratio of the number of damaged cells to healthy cells was obtained through the CA model of cellular inflammatory responses. This ratio, in turn, affected the change in the Young's modulus of elasticity of the alveolar sac tissue. The stiffness for the injured tissue was about 25% less than that of the normal tissue [11]. The decrease in the stiffness of the injured tissue was assumed to be proportional to the ratio of the number of damaged cells to healthy cells. The time steps for the organ- and cellular-level models were 0.5 s and 4 h, respectively. The coupling time between the organ-level, tissue-level, and cellular-level models was 4 h. Figure 1 shows the computational domains and exchanging information between the organ-, tissue-, and cellular-level models for an investigation of inflammatory responses at the alveolar sac during mechanical ventilation.

The simulations were carried out to investigate inflammatory responses at the alveolar sac during mechanical ventilation. The simulations were performed until 100 iterations of coupling time, about 400-h real time. The flow waveform from mechanical ventilation was a constant flow waveform with flow rate of 60 l/min. A mechanical ventilation setting of 1400-cc tidal volume was chosen for the analyses. All the simulations were carried out on a desktop Dell computer with dual processors with no load balancing between different types of analysis. The transfer of data between organ and tissue levels is carried out manually rather than automatically exchanged between softwares, which will be considered in the future.

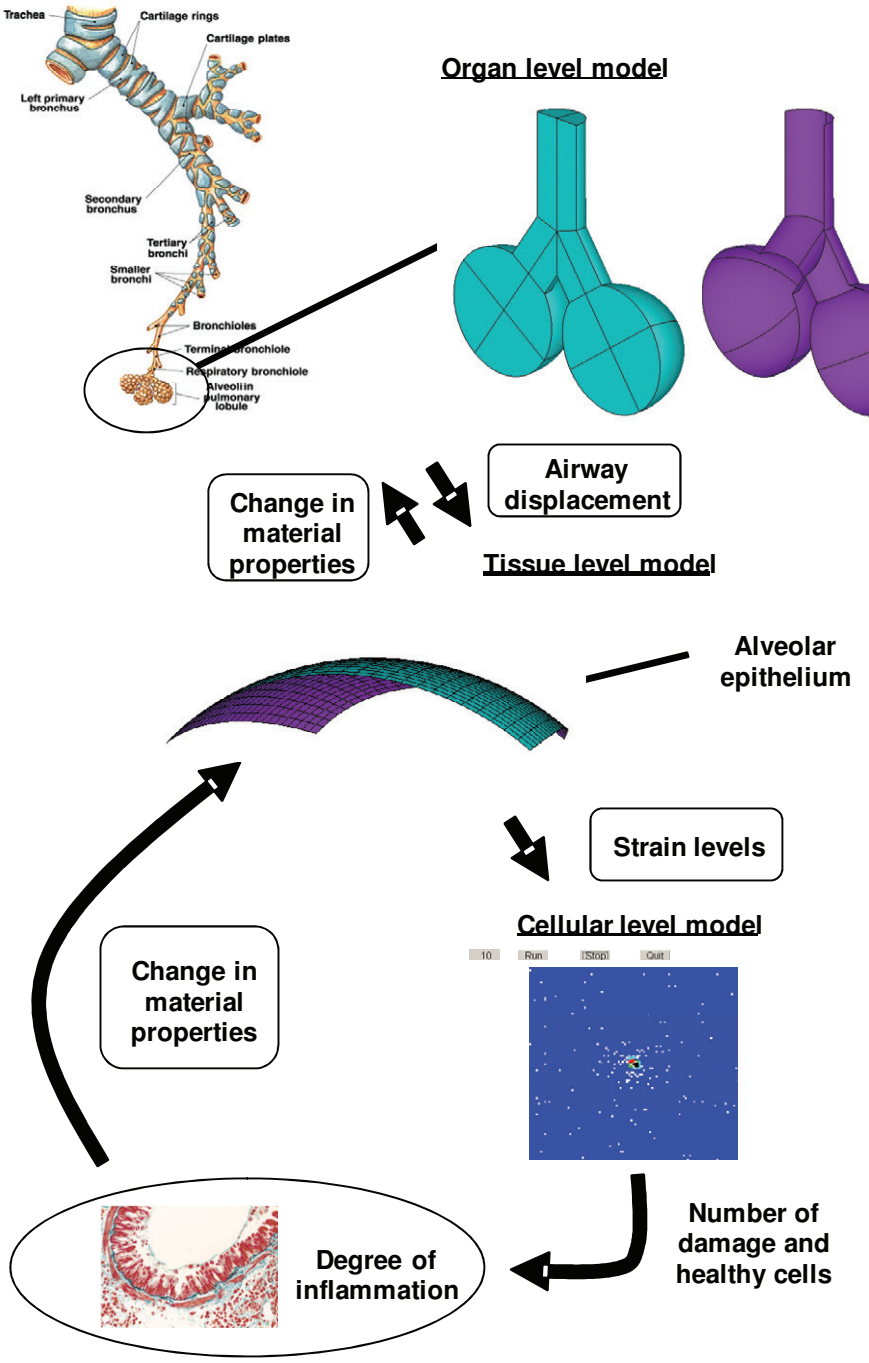


Figure 1. A schematic diagram of the multiscale model of inflammatory responses at the alveolar sac during mechanical ventilation based on the multiscale modeling framework

4. Results and Discussion

The strain distributions in the alveolar sac are shown in Figure 2. The lowest strain was observed at the beginning on the sac. The average strain in the sac was about 26-33%. The pressure in the sac expanded the sac during the inhalation. Figure 3 shows inflammatory responses at the alveolar sac during mechanical ventilation. The number of immune cells increased with increasing time step due to the strain levels from mechanical ventilation. This increase in activated immune cells damaged healthy cells. These damaged cells in turn induced more activated immune cells and these activated immune cells caused more damage cells. The number of healthy, damaged, dead, immune cells, and strain levels as a function of time step is shown in Figure 3. As can be seen from this figure, the number of immune cells increased with increasing time step. This increase in immune cells caused damage cells to dramatically increase. This increase in damage cells increased the strain levels in the alveolar sac because the tissue was less stiff during the injury. The high strain levels, in turn, induced more activated immune cells. Overall, the simulation results support the clinical practice observation that high tidal volume can cause ventilator-associated lung injury (VALI) at the alveolar sac due to high level of activated immune cells.

Table 1 summarizes the results obtained from organ, tissue and cellular level models. It can be seen from Table 1 that at the organ level, a maximum of 55% von-Mises strain is seen and this is comparable to those obtained experimentally by Sinclair et al. [12], who showed that the strain ranges of 15%-65% occur in the airway diameters of 200-2500 μm. From the tissue level model, the maximum strain occurs in the epithelial layer. Using these strains in the cellular model, a ratio of 0.6-1.8% of damaged to healthy cells was obtained. A summary remark of major findings from each of the results at various levels is given in Table 1.

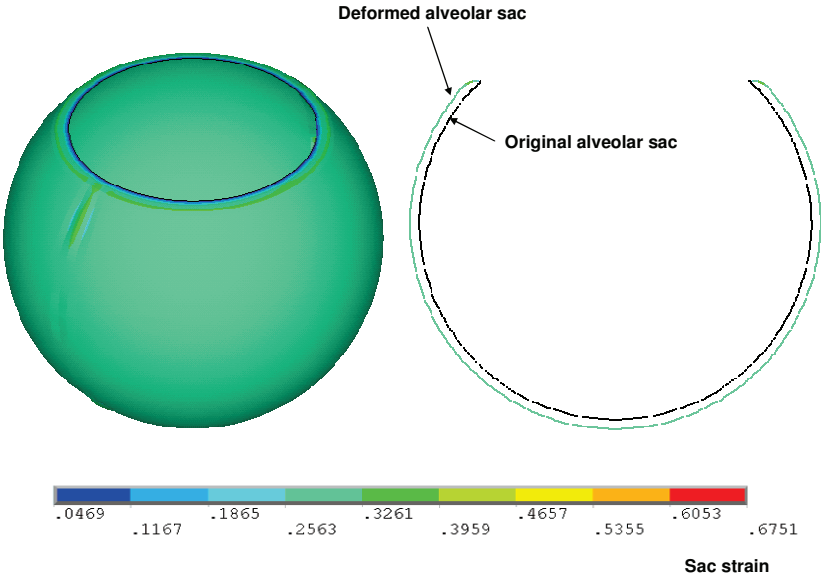


Figure 2. Airway strain in the alveolar sac at the end of inhalation for airflow rates of 60 L/min with a constant flow waveform

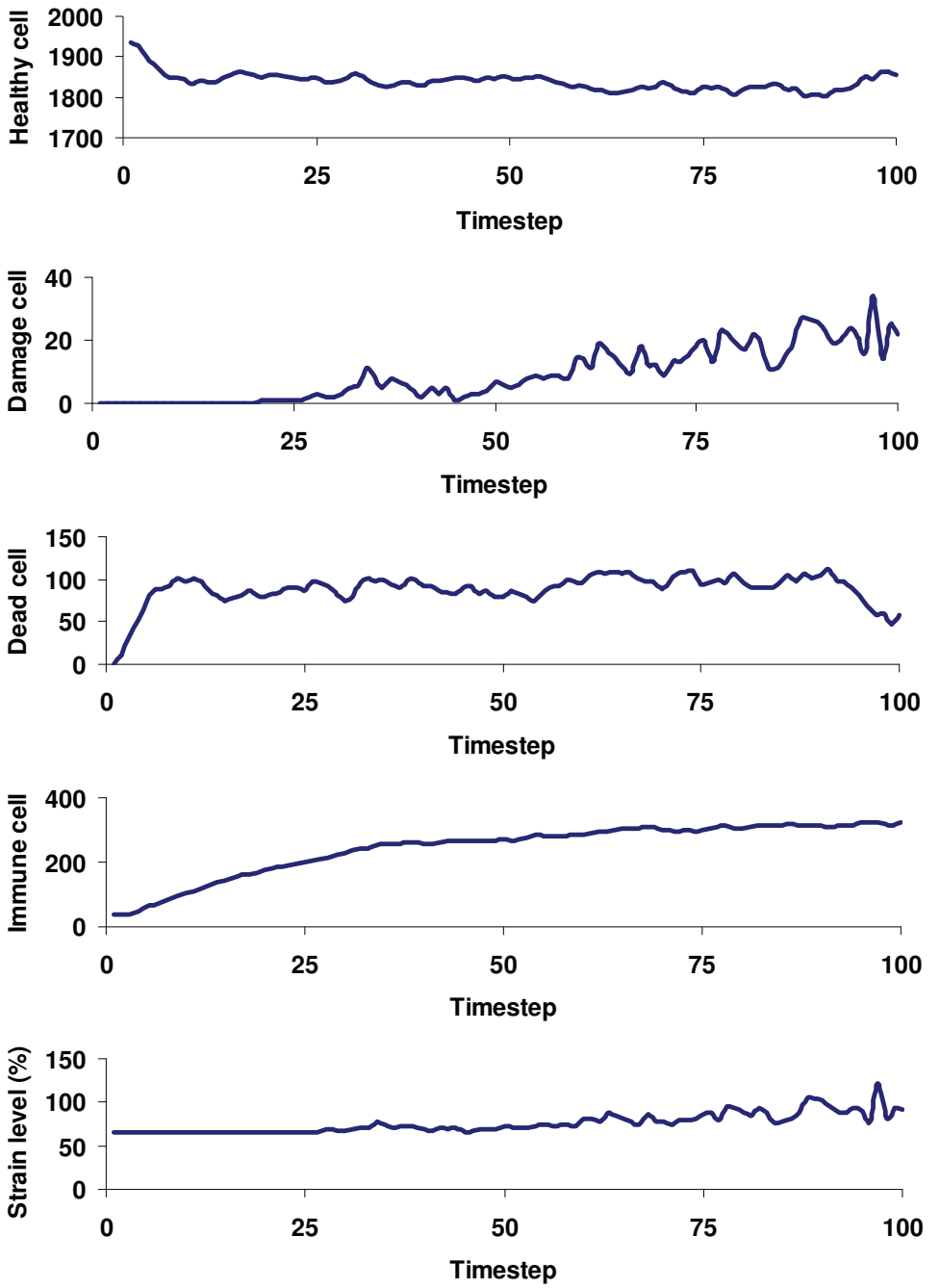
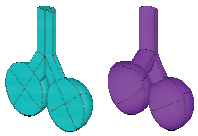
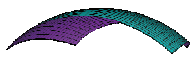
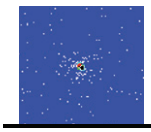


Figure 3. The number of healthy, damage, dead, immune cells, and strain levels as a function of time step

Table 1. Summary of the simulation results from the multiscale model of the airway inflammation induced by mechanical ventilation

Level	*Output*	*Significance*	*Remarks*
Organ 	55% maximum von Mises strain, 21% maximum 1st principal strain, and 20% change in sac diameter; Previous studies by Sinclair et al [12] in the airway diameter of 200-2500 μm showed that maximum circumferential strains were in the ranges of 15-65%	Might cause tissue injury due to high strain levels (see cellular level)	Finding is specific to this geometry. This might be different when the whole alveoli is considered (need further studies)

Level	*Input*	*Output*	*Significance*	*Remarks*
Tissue 	Airway displacement from the organ level and material properties of each layer from previous experiments	55% maximum von Mises strain in the epithelial layer	Might cause tissue injury/damage (see cellular level)	Further studies on the effect of geometry and viscoelasticity property are needed
Cellular 	Strain levels from the tissue level and CA rules based on previous experiments	Ratio of damaged to healthy cells was about 0.6-1.8%	Might cause tissue injury due to high concentration of activate immune cells	Need to correlate the strain level with degree of inflammation and tissue properties

5. Concluding Remarks

The framework for developing a multiscale model of the lung airway inflammation was described. The multiscale model of the airway consists of the organ-level, tissue-level, and cellular-level models. This multiscale model of the airway was employed to study inflammatory responses at the alveolar sac during mechanical ventilation. The simplified model of the alveolar sac was chosen for the analysis. The airway displacements from the organ-level model were transferred to the tissue-level model for distributions of strain levels. The strain levels in the epithelial layer from the tissue-level model were then transferred to the cellular-level model for inflammatory responses due to strain levels. The injury at the cellular level, in turn, modulated change in material properties of the tissue at the tissue and organ levels. The simulation results showed that high tidal volume (1400 cc) during mechanical ventilation can cause tissue injury due to high concentration of activated immune cells. At low tidal volume during mechanical ventilation (700 cc) can prevent tissue injury during mechanical ventilation and can mitigate tissue injury from the high tidal volume ventilation. The information obtained from this multiscale model could provide useful information on VALI and the new ventilation strategies could be developed to prevent VALI.

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